Autonomic dysfunction in cardiovascular system of type 2 diabetic mellitus – a bedside evaluation

Dissertation submitted in partial fulfillment of regulation for the award of M.D.

Degree in General Medicine (Branch I)

The Tamilnadu
Dr. M.G.R. Medical University

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Coimbatore Medical College & Hospital
Coimbatore - 641 014

certificate

*This is to certify that the dissertation entitiled "**Autonomic Dysfunction in cardiovascular system of Tyoe 2 diabetic mellitus- A bedside evaluation"** , herewith submitted by **Dr NAVUKKARASU.P**, post graduate in General Medicine Coimbatore Medical College Hospital is the record of a bonafide research work carried out by him under our guidance and supervision from July 2006 to June 2008.*

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DECLARATION

I solemnly declare that the dissertation titled **"Autonomic dysfunction in cardiovascular system of type 2 diabetic mellitus – a bedside evaluation"** was done by me at Coimbatore Medical College hospital from July 2006 to June 2008 under the guidance and supervision of **Prof Dr. UMAKANTHAN.K MD**, Unit Chief and Head of Department.

This dissertation is submitted to the Tamilnadu Dr. MGR Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

DR. NAVUKKARSU.P

Place : Coimbatore

Date : 01.12.2008

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ETHICS COMMITTEE

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CONTENTS

INTRODUCTION

Autonomic nervous system involvement in diabetes mellitus was described by Rundles in 1945. The study of autonomic nervous system involvement in diabetes mellitus is of special interest because this appears to have increased mortality. About 50 % of patients with autonomic dysfunction of five years duration die of sudden cardio respiratory arrest

In 20 to 40% of all diabetes mellitus patients some abnormalities of autonomic function is present. Diabetic autonomic neuropathy can involve both sympathetic and parasympathetic nervous system. Parasympathetic abnormalities appear earlier and sympathetic innervations may remain intact even in presence of severe Parasympathetic damage.

Abnormalities in bowel and bladder function and impotence has been ascribed to involvement of autonomic nervous system in diabetes mellitus

The integrity of autonomic nervous system can be assessed with several simple tests which are based on cardiovascular reflexes. These tests are dependent on the response of heart rate and blood pressure to a variety of stimuli.

Autonomic function test reflecting parasympathetic function

1 Heart rate response to Valsalva maneuver

2 Heart rate variation during deep breathing

3 Immediate heart rate response to standing

Autonomic function test reflecting sympathetic function

1 Blood pressure response to standing

2 Blood pressure response to sustained hand grip

3 These results are correlated to duration of disease and with age of patient.

AIMS OF STUDY

- To determine various aspect of autonomic neuropathy in diabetic population using series of standardized test.
- To interpret the different type of presentation of autonomic neuropathy in diabetes mellitus
- To study the clinical presentation of autonomic neuropathy in diabetes mellitus

REVIEW OF LITERATURE

Diabetes mellitus is defined as a group of common metabolic disorders that share the phenotype of hyperglycemia. The factors contributing to hyperglycemia include reduced insulin secretion, insulin resistance, decreased glucose utilization and increased glucose production. Diabetes mellitus is caused by complex interaction of genetics, environmental factors and life style choices (1). The disease has particular predilection for micro vascular complications and tendency for macro vascular complication. Hence diabetes is a metabolic cum vascular disease.

Historical background of understanding of diabetes can be traced as early as third century B.C. The Ebers papyrus written about 1550 B.C, the prescription to drive away the passing too much urine recommends bones, wheat grains, green lead earth and water. The ancient physicians recorded the observation that if too many ants swarm around spot of urine if the person is diabetic (2).

Two Greek physicians **Galen and Arateus**[2] of Cappadocia in 130 – 201 A.D classified acute and chronic diseases. They described meaning of diabetes as siphon liquefaction of flesh and bones in urine.

Ancient Hindu document by **Susrutha**[2] in India in 400 BC described diabetic syndrome characterized by honeyed urine.

Langerhans (1869) discovered ilets which was later named as islets of Langerhans. In 1893 he suggested that collection of interacinar cells as gland of

secretion within the pancreas.[2]

Jean-de-meyer (1910)[2] suggested that the pancreatic secretion lacking in diabetes be called insulin to denote the origin from insulae on langerhans.

In 1921-22 **Fredrick Banting** surgeon, **John Macleod** physiology professor, **Charles Best** graduate and **J.b.Collip** skilled chemist fulfilled all criteria by demonstrating therapeutically active insulin preparation for treatment of diabetes mellitus.[2]

Classification of diabetes mellitus[1]

- **Type 1** diabetes due to absolute insulin deficiency (beta cell destruction)
- **Type 2** diabetes range from predominantly insulin resistance with relative insulin deficiency to predominantly insulin secretory defect with insulin resistance (1).
- **Other specific types of diabetes**

A. Genetic defect of beta cell function characterized by mutation

1. Hepatocyte nuclear transcription factor (MODY 1)
2. Glucokinase (MODY 2)
3. HNF-1 α (MODY 3)
4. Insulin promoter factor (MODY 4)
5. HNF-1 β (MODY 5)
6. Neuro D1 (MODY 6)
7. Mitochondrial DNA
8. Proinsulin or insulin conversion

B. Genetic defect in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-mendenhall syndrome
4. Lipodystrophy syndromes

C. Diseases of exocrine pancreas

1. Pancreatitis
2. Pancreatectomy
3. Cystic fibrosis
4. Hemochromatosis
5. Fibrocalculus pancreatopathy

D. Endocrinopathies

1. Acromegaly
2. Cushing’s syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma

E. Drug induced

1. Pentaminidine
2. Glucocorticoids
3. Nicotinic acid
4. Thyroid hormone
5. Beta adrenergic agonists
6. Thiazides
7. Beta blockers
8. Phenytoin

F. Infections

1. Congenital rubella
2. Cytomegalovirus
3. Coxsackie virus

G. Immune mediated diabetes

1. Stiff-man syndrome
2. Anti-insulin receptor antibodies

H. Genetic syndrome associated with diabetes

1. Down’s syndrome
2. Klinefelter’s syndrome
3. Turner’s syndrome
4. Wolfram s syndrome

5. Prader-willi syndrome
6. Myotonic dystrophy

- **Gestational diabetes mellitus**

DIAGNOSTIC CRITERIA

I. Random plasma glucose or more than equal to 200mg/dl (11 mmol/dl) with classic symptoms polyuria, polydipsia, and weight loss.[1]

II. Fasting plasma glucose (no caloric intake for at least 8 hours) more than or equal to 126mg/dl (7 mmol/dl)

III. 2 hour plasma glucose during oral glucose tolerance test more than or equal to 200mg/dl (11 mmol/dl)

Classification of diabetic neuropathy[1]

1. **Somatic**
   - Polyneuropathy
   - Polyradiculopathy
   - Mononeuropathy
   - Mononeuropathy multiplex
2. **Visceral – autonomic neuropathy**
   - Cardiovascular
   - Gastrointestinal

- Sudomotor
- Genitourinary
- Hypoglycemia unawareness

POLYNEUROPATHY

Polyneuropathy is predominantly sensory. Clinical features are hyperesthesia, paresthesia, dysesthesia, numbness, tingling sensation, burning that begins in feet and spreads proximally, bilateral glove and stoking loss of sensation, diminished vibration sense, absent ankle jerk, abnormal position sense and ulceration over ball of the foot.

POLYRADICULOPATHY

Polyradiculopathy involves one or more nerve roots causing severe disabling pain with motor weakness. Intercostal or truncal radiculopathy causes pain over thorax or abdomen.

MONONEUROPATHY

This includes dysfunction of isolated cranial nerve or peripheral nerve. Clinically patient presents with pain or weakness in distribution of single nerve.

- ❑ Trochlear (fourth) or abducens (sixth) - Ptosis and opthalmoplegia

- ❑ Facial nerve (seventh cranial nerve) - Bells palsy

MONONEUROPATHY MULTIPLEX

Subacute affection of multiple nerves simultaneously leads to mononeuritis multiplex .[6]

Causes

- Diabetes
- Polyarteritis nodosa
- Chrug strauss syndrome
- Lymes disease
- Leprosy
- Cryoglobulinemia

DIABETIC AMYOTROPY

Involvement of lumbar plexus or femoral nerve causes pain in thigh or hip and is associated with muscle weakness in hip flexors or extensors.

Functional Organization of Autonomic Nervous System[6]

The Autonomic nervous system is an efferent system that innervates vascular and visceral smooth muscle, exocrine and endocrine glands, parenchymal cells throughout the various organ systems in the body. The distribution of blood flow and maintenance of tissue perfusion, regulation of volume and composition of extra cellular fluid, the expenditure of metabolic energy and supply of substrate and the activity of visceral smooth muscle glands.

Anatomic Organization of Autonomic Nervous System

The Autonomic nervous system is located in ganglia outside central nervous system give rise to postganglionic autonomic nerves that innervates organs and tissue throughout the body.

Afferent Autonomic Nervous System

Sympathetic Nervous System: Terminate in spinal cord in intermediate zone grey matter in relation to preganglionic neurons

Function : Important in appreciation of visceral pain.

Parasympathetic Nervous System : afferent fibers from mouth and pharynx and respiratory, cardiac and gastrointestinal system, terminate in nucleus of tractus solitarius through facial, glossopharyngeal and vagus nerve.

Function : important in maintaining the visceral reflexes.

Autonomic nervous system maintains the visceral and homeostatic function essential to life. Both sympathetic and parasympathetic system is regulated by limbic system, hypothalamus, and ventricular formation. Fibers from these structures descend to synapse with preganglionic neurons in intermediolateral column T_1 to L_2 (Sympathetic - thoracolumbar).

Cranial nuclei occulomotor, facial, glossopharyngeal, vagus, and S_2-S_4 (Parasympathetic - craniosacral)

NEUROTRANSMITTER

Acetylcholine is preganglionic neurotransmitter for both division of autonomic nervous system as well as postganglionic neurotransmitter of the parasympathetic system. Cholinergic neuron also supplies sweat glands (eccrine), and some blood vessel supplying skeletal muscle.

DIRECT EFFECT

Catecholamines on cardiovascular system stimulate vasoconstriction in the subcutaneous, mucosal, splanchnic, and renal vascular beds by an alpha receptor mediated mechanism

Catecholamines influence the secretion of variety of hormones including renin, insulin, glucogon, cacitonin, parathormone, thyroxine, gastrin, erythropoietin, progesterone, and testosterone.

PHYSIOLOGY OF AUTONOMIC NERVOUS SYSTEM

Autonomic neuropathy pain

Gate theory of pain (melzack and wall) proposed that interneuron's in substantia gelatinosa of spinal cord exerts a modulating effect upon sensory input before this activates the first central transmission cells in dorsal horn of the cord which in turn stimulates central mechanism responsible for response and perception. Tonic activity in small C fibers keep open the gate and allow the transmission of painful sensation, activity in A fibers tends to close the gate. Perception of pain depends upon relative

activity in large and small fibers. Counterirritant as by scratching or rubbing increase large fiber discharge and reduces pain.

PHYSIOLOGY OF VALSALVA MANEUVER

There are important effects of respiration on the heart and circulatory system.

In central nervous system there are interactions between respiratory pacemakers and efferent autonomic tone which directly affect heart rate and blood pressure.

These pacemakers induce variation in systemic blood pressure at same period as the frequency of respiration. These blood pressure waves termed as Traube - Hering waves, who explained it.[5]

During inspiration the pacemaker waves stimulates efferent sympathetic nerve.

Vagal tone is also centrally mediated and related to respiration. Vagal tone decreases during expiration and increases during inspiration through baroreceptors and stretch receptors.

Mechanically during inspiration intrathoracic pressure is reduced which results in increased right atrial inflow. Left atrial inflow is transiently reduced consequent to rise in pulmonary vascular capacity leading to fall in aortic blood pressure in early inspiration.

During expiration systemic venous return reaches the left atrium which increases left ventricular outflow, results in an increase in systemic pressure retuning blood pressure to its peak level.

During inspiration heart rate increases due to central factors and brain bridge effect. Heart rate is reduced in late inspiration and early expiration.

CARDIOVASCULAR SYSTEM

Parasympathetic effects of heart are mediated by vagus nerve. Acetylcholine reduces rate of spontaneous depolarization of sinus node and reduces the heart rate.

GASTROINTESTINAL TRACT

Parasympathetic innervation of gut is via vagus nerve and the pelvic sacral nerve. The parasympathetic nervous system increases the tone of gastrointestinal smooth muscle, increases peristaltic activity and relaxes gastrointestinal sphincter. The classic concept of diabetic diarrhea is nocturnal diarrhea or incontinence of feces in night without knowledge to patient. The mechanism of diabetic diarrhea has not been established. The possibilities are;

- Autonomic neuropathy
- Bacterial overgrowth in stomach and small intestine
- Pancreatic exocrine dysfunction
- Intestinal muscular abnormalities

ORTHOSTATIC HYPOTENSION

Standing up results in pooling of blood in dependant part of body due to effect's of gravity. Sympathotonic hypotension rare form of orthostatic hypotension of neurogenic origin associated with marked tachycardia when patient stands. The sympathetic nervous system seems to react normally to postural changes, but there is

impaired response of the effect or organ to nor epinephrine causing a drop in blood pressure despite the increased pulse rate

NEUROGENIC BLADDER

There is reduced frequency in juvenile diabetics with vesical involvement (of autonomic neuropathy) due to increased bladder capacity.

IMPOTENCE

Impotence is neuropathic manifestation of diabetes. In survey of 200 diabetics, neurogenic bladder as a result of autonomic neuropathy has strongly association with impotence. Libido persists initially, but in some tends to decrease while in others it may not diminish for years.

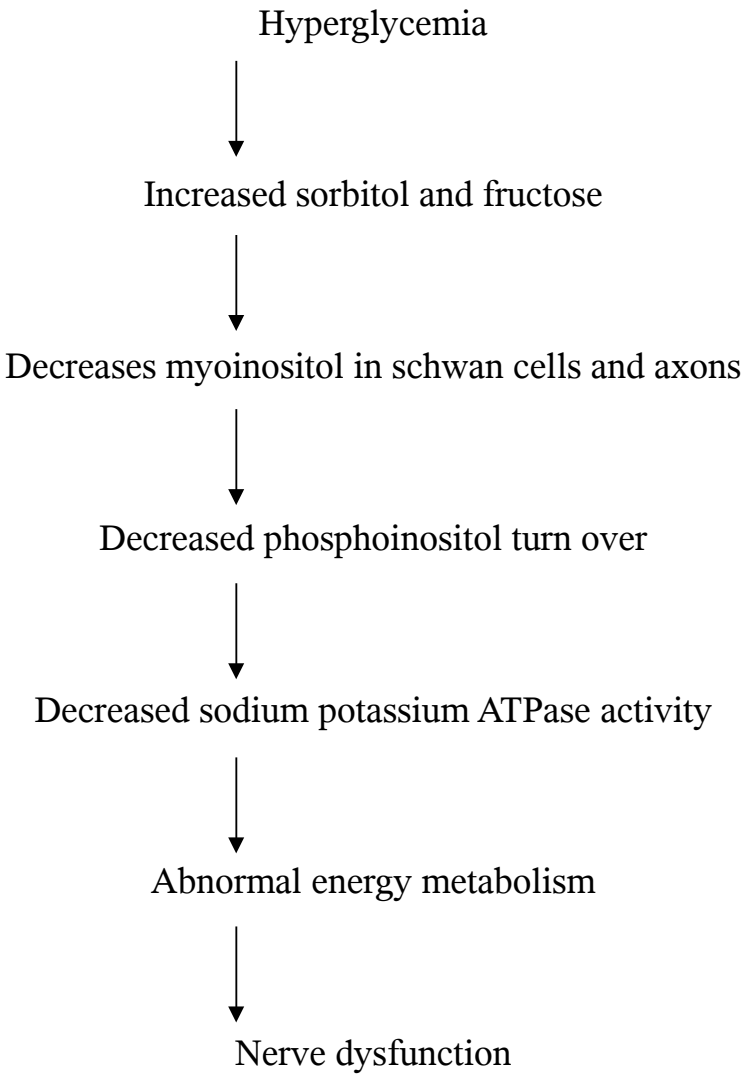
Other neurological disorder may also be responsible for impotence with retention of libido. A disease affecting the spinal cord or with local involvement of parasympathetic plexus prevents the reflex or erection. Some of these are tabes dorsalis, syringomyelia, multiple sclerosis, spinal cord tumors, Pernicious anemia and myelitis. Vascular disorders such as thrombosis of aortic bifurcation or arteriosclerosis may cause impotence.

The equivalent of erectile failure in women is absence of vaginal lubrication during intercourse. A distinct entity clitoral neuropathy has been reported. This is usually mistaken for candidal vaginitis, since it produces Paresthesias over genitalia. Adequate control of diabetes and prompt treatment of candidal vaginitis relieves dyspareunia and orgasmic dysfunction.

PATHOPHYSIOLOGY OF PERIPHERAL NEUROPATHY

- Myelin sheath is most susceptible element.
- Axonal degeneration occurs due to repeated demyelination and remyelination which leads to onion bulb formation of schwan cells and fibroblast.
- Lesions are found in posterior column of spinal cord posterior roots, rami communicants and sympathetic ganglia.
- Basement membrane of intraneural capillaries are thickened and duplicated (6).

PATHOPHYSIOLOGY OF AUTONOMIC NEUROPATHY



CLINICAL FEATURES OF AUTONOMIC NEUROPATHY

Autonomic nervous system abnormalities can affect a variety of system in the body.

CARDIOVASCULAR SYSTEM

Autonomic neuropathy of cardiovascular system causes postural hypotension, resting tachycardia, loss of heart rate variation, and sudden cardio respiratory arrest.

GASTROINTESTINAL

Autonomic neuropathy of gastrointestinal system causes

- Nocturnal diarrhea due to gastroparesis
- Abdominal fullness due to gastric atony
- Dysphagia due to esophageal atony

UROGENITAL

- Urinary incontinence, recurrent infection due to atonic bladder
- Impotence, retrograde ejaculation, loss of testicular sensation

RESPIRATORY SYSTEM – Respiratory Arrest

Pupilary abnormalities

Autonomic neuropathy causes reduced resting diameter, delayed or absence response to light, resistance to mydriatics, and diminished hippus.

VASOMOTOR

- Loss of skin vasomotor responses
  - Peripheral vascular changes
  - Charcot's arthropathy

- Dependent oedema

SUDOMOTOR

- Hyperhydrosis of upper extremities and anhydrosis of lower extremities
- Gustatory sweating
- Nocturnal sweats without hypoglycemia
- Fissures in the feet

HYPOGLYCEMIC UNAWARENESS

- Decreased catecholamine release with loss of warning symptoms of hypoglycemia

- Decreased pancreatic glucagon and pancreatic polypeptide release

CAUSES OF AUTONOMIC DYSFUNCTION

The causes of autonomic dysfunction are many some of the common causes are listed below (1).

I. AUTONOMIC DISORDERS WITH BRAIN INVOLVEMENT

A. Associated with multisystem degeneration

1. Multisystem degeneration: autonomic failure clinically Prominent
    a) Multisystem atrophy
    b) Parkinsons disease with autonomic failure
    c) Diffuse lewy body disease

2. Multisystem degeneration: autonomic failure clinically not Prominent
    a) Parkinsons disease
    b) Other extrapyramidal disease
        i. Spinocerebellar atrophies
        ii. Machado-joseph disease
        iii. Progressive supranuclear palsy
        iv. Corticobasal degeneration

B. Unassociated with multisystem degeneration

1. Disorders mainly due to cerebral cortex involvement
    a) Frontal cortex lesion
    b) Complex partial seizures

2. Disorders of limbic and paralimbic circuits

   a) Shapiro's syndrome corpus callosum agenesis, hyperhydrosis and hypothermia

   b) Autonomic seizures

3. Disorders of hypothalamus

   a) Wernicke-korasakoff syndrome

   b) Diencephalic syndrome

   c) Neuroleptic malignant syndrome

   d) Serotonin syndrome

   e) Antidiuretic hormone syndromes (diabetes insipidus, inappropriate ADH)

   f) Fatal familial insomnia

   g) Disturbance of appetite

   h) Disturbance of sexual function

   i) Disturbances of gastric function

   j) Horner's syndrome

4. Disorders of brainstem and cerebellum

   a) Posterior fossa tumors

   b) Syringobulbia and arnoldchiari malformation

   c) Cardiac arrhythmias

   d) Central sleep apnea

e) Baroreflex failure

II. AUTONOMIC DISORDERS WITH SPINAL CORD INVOLVEMENT

a) Traumatic tetraplegia

b) Syringomyelia

c) Subacute combined degeneration

d) Multiple sclerosis

e) Amyotrophic lateral sclerosis

f) Tetanus

g) Stiff-man syndrome

h) Spinal cord tumors

III. AUTONOMIC NEUROPATHIES

A. Acute/subacute autonomic neuropathies

Subacute autonomic neuropathy

a) Subacute paraneoplastic autonomic neuropathy

b) Gullian-barre syndrome

c) Botulism

d) Porphyria

e) Drug induced autonomic neuropathies

f) Toxic autonomic neuropathies

B. Chronic peripheral autonomic neuropathies

1. Distal small fiber neuropathy
2. Combined sympathetic and parasympathetic failure
    a) Amyloid
    b) Diabetic autonomic neuropathy
    c) Autoimmune autonomic neuropathy
    d) Sensory autonomic neuropathy
    e) Familial dysautonomia (Riley-Day syndrome)

MANAGEMENT OF AUTONOMIC DYSFUNCTION IN DIABETES MELLITUS

1. Management of Postural hypotension[1]

Non-pharmacologic approach

1. High-salt diet (10 to 20 grams per day)
2. High fluid intake (2 liters per day)
3. Elevate head of bed 4 inches
4. Compression garments – Elastic stockings
5. Correct anemia
6. Patient education of mechanism
    a) Volume status
    b) Resistance
    c) Capacitance bed
    d) Autoregulation

7. Patient education of stressors of orthostatic hypotension

   a) Influence of meals

   b) Standing

   c) Exercise

   d) Heat

   e) To sit with legs dangling over the edge of bed for several minutes before attempt to stand in the morning.

8. To learn physical counter maneuvers

   a) To maintain contraction of leg muscle for 30 seconds

   b) Leg crossing

Such maneuvers compress leg veins and increase systemic resistance

PHARMACOLOGIC TREATMENT [1]

1) Midodrine – alpha agonist 5 to 10 mg thrice daily

Some patients respond best to decremental dose like 15 mg on awakening, 10 mg at noon and 5 mg in the afternoon. It should not be given after 6 P.M. Side effects are Pruritis, uncomfortable piloerection and supine hypertension.

2) Fludrocortisone – 0.1 to 0.3 mg per day in two divided doses

It enhances renal sodium conservation and increases the sensitivity of arterioles to nor epinephrine. Side effects are Supine hypertension and hypokalemia.

3) Pyridostigmine

It improves orthostatic hypotension without causing supine hypertension by enhancing ganglionic transmission maximum during orthostatic and minimum in supine position.

MANAGEMENT OF POSTPRANDIAL HYPOTENSION[1]

Frequent small low-carbohydrate meals may diminish splanchnic shunting of blood after meals

Prostaglandin inhibitors – ibuprofen or indomethacin

Midodrine – 10mg along with meals

Octreotide - (25µg twice daily to 200µg thrice daily) somatostatin analogue inhibits the release of gastrointestinal peptides. (Gastrointestinal peptide is vasodilator which will cause hypotension).

MANAGEMENT OF GASTROINTESTINAL DYSFUNCTION

Good glycemic control will improve gastric function and autonomic neuropathy

Smaller, more frequent meals, fiber rich, easier to digest, low in fat, will minimize symptoms of gastroparesis

Drugs for gastroparesis

a) Cisapride 10 to 20mg before each meal

b) Bethanechol 10 to 20 mg before each meal

c) Dopamine agonist domperidone 10 to 20 mg or metaclopramide 5 to 10 mg before each meal.

Diabetic diarrhea

In absence of bacterial growth, can be treated with

a) Loperamide

b) Octreotide 50 to 75 µg thrice daily subcutaneously

c) Clonidine at higher doses 0.6 mg thrice daily

MANAGEMENT OF BLADDER DYSFUNCTION AND URINARY RETENTION

Bladder emptying is improved with cholinergic agonist Bethanechol (reduces residual urine) and phenoxybenzamine. Bladder neck surgery to minimize the urethral resistance

MANAGEMENT OF IMPOTENCE

a) Injection of papaverin 40 to 80 mg directly into corpus cavernosum improves neuropathic impotence.

b) Vasculogenic impotence due to small vessel disease needs bypass surgery which relieves proximal vessel occlusion.

c) Semi rigid or malleable prosthesis and inflatable prosthesis are available.

d) Recently 'Erect aid systems' with vacuum fitting have found a high degree of patient acceptance.

e) Lubricants like K.Y jelly during intercourse helps overcome dry coitus.

CARDIO RESPIRATORY ARREST

Sudden and unexpected deaths occur in diabetics with autonomic neuropathy this may be due to cardio respiratory arrest in association with hypoxia. any diabetics who has autonomic neuropathy is a considerable anesthetic risk and particular care to be taken during and after the operation to try to prevent such episodes, which may be due to sudden changes in inspired oxygen saturation.

PREVENTION OR REVERSAL OF AUTONOMIC DAMAGE

By the time the symptoms developed autonomic nerve damage is probably irreversible and carries poor prognosis.

a) Good metabolic control can achieve some reversal of autonomic abnormalities.

b) Aldose reductase inhibitors sorbinil or epalrestat 250 mg daily improves pain numbness, and motor nerve conduction velocity.

c) Myoionositol rich in sea food and vegetables like drumstick can achieve some reversal of autonomic damage.

METHODS OF TESTING AUTONOMIC DYSFUNCTION

Ewing-et-al (1978) proposed five simple tests to assess autonomic neuropathy based on cardiovascular reflexes. These are

1. Valsalva maneuver
2. Heart rate variation to deep breathing
3. Heart rate response to standing
4. Postural variation of blood pressure
5. Hand grip test (In normal person diastolic blood pressure variation > 16mm)

The first three test assess cardiac parasympathetic function and last two test mainly sympathetic function

1. Valsalva maneuver

It consists of forced expiration against closed glottis. This procedure by producing a rise in intrathoracic pressure causes acute drop in effective filling pressure of the heart with consequent changes in stroke volume (5).

CLINICAL PROCEDURE

First resting electrocardiogram is recorded. The procedure is explained to the patient who is trained to blow and maintain the column of mercury at 40mm of mercury in sphygmomanometer. After satisfactory training, continuous electrocardiograph is

recorded during the maneuver for 10 to 20 seconds and immediately after the maneuver for 30 seconds.

Valsalva ratio is obtained by dividing longest RR interval after maneuver to shortest RR interval during maneuver.

PHASES OF VALSALVA MANEUVER[1]

There is a sharp initial rise of blood pressure equivalent to the rise in the intrathoracic pressure during the phase of forced expiration (phase1).

There after the pulse pressure diminishes gradually and the heart rate raises due to a fall in stroke out put (phase 2).

On release of strain there is a sudden drop of blood pressure equivalent to the fall in intra thoracic pressure, and for a second or two pulse pressure may be small (phase 3). Rise in blood pressure can be seen if period of strain is long.

With restoration of normal condition the heart fills properly and cardiac output increases. But before the pulse pressure widens the heart rate slows (vagal stimulation) due to reflex vasoconstriction initiated by small pulse pressure stimulating aortic and carotid baroreceptors (phase 4).

Because of apparent value of this test, a bed side version was devised by Levin-et-al. this is conveniently achieved by blowing up column of mercury and maintaining pressure of mercury column for ten seconds. Valsalva ratio is obtained by calculating ratio of maximum tachycardia to bradycardia.

2. Heart rate response to deep breathing

Page and walkins (1977) found that in absence of autonomic symptoms, mean beat to beat variation is slightly impaired perhaps indicating one of the earliest manifestation of autonomic neuropathy.

Sinus arrhythmia is beat to beat variation of heart rate. This is controlled through autonomic nervous system. It is very often found in healthy children. In adult it becomes prominent after deep voluntary respiration.

During inspiration impulses arise from lungs which reflexly inhibit vagal tone, causing increase in heart rate. It can be quantified and used as a bed side test by measuring the difference between maximum and minimum heart rate during slow deep breathing (6 breaths per minute).since beat to beat variation is mediated by vagus, it is abolished or reduced in patients with autonomic neuropathy.

Clinical Procedure

Heart variation with deep breathing was recorded to the procedure by using electrocardiograph. The subject lies quietly in supine position and is connected to electrocardiograph machine to record heart rate with lead 2. The patient is instructed to breath deeply at a rate of 6 breaths per minute a rate that produce maximum variation in heart rate, and simultaneous electrocardiograph recorded.

Heart rate was compared for the shortest RR interval during inspiration and longest RR interval during expiration. Beat to beat variation is calculated by measuring the difference between the heart rates during inspiration and expiration.

3. Orthostatic variation of blood pressure

It has long appreciated that postural hypotension is a sensitive indicator of autonomic dysfunction. Berner (1952) has confirmed by experiments. Friedman-et-al (1972) considering vasomotor tone studies in 19 patients defined postural hypotension as a fall of more than 30mm mercury in systolic pressure when the patient stand erect rapidly.

Clinical procedure

After 3 minutes of comfortable relaxation in supine position basal blood pressure is recorded over right arm. Three values are taken at intervals of one minute in between then the patient is asked to stand erect rapidly with in few seconds. Blood pressure is recorded. The cuff is completely deflated in between recordings

4. Heart rate response to standing

Change from horizontal to vertical posture produces a reflex tachycardia maintained by autonomic nervous system Bennett (1976) concluded that sympathetic nervous system is intact if there is maintenance of blood pressure on standing associated with moderate tachycardia. Page-et-al observed that the peak rise in heart rate occurs 10 to 20 seconds after standing up from supine position. Heart rate then stabilizes at a rate still higher than in supine position.

The peak rate increases varies but it is almost always greater than 15 beats per minute but in patients with autonomic neuropathy and improved cardiovascular reflexes, reflex tachycardia is diminished or lost in autonomic neuropathy.

Clinical procedure

Electrocardiograph is first recorded in supine position and then the subject is asked to assume erect posture rapidly, electrocardiograph recording is being continued. Recording is done for 40 to 50 cardiac cycles RR ratio is obtained by dividing the RR interval of 30^{th} beat to the RR interval of 15^{th} beat.

5. Blood pressure variation with sustained hand grip

Sustained muscular exercise normally causes rise in heart rate, cardiac output and arterial pressure. This response is secondary to rise in peripheral vascular resistance which is mediated by sympathetic and parasympathetic nervous system.

A simple test based on this reflex uses a hand grip dynamometer standardized at 30% of maximum voluntary contraction with measurement of blood pressure during hand grip. Patients with autonomic neuropathy have an abnormal small diastolic blood pressure rise. Ewing defined the response of diastolic pressure rise of 16mm of mercury or above as normal, less than 10mm of mercury as abnormal.

Clinical procedure

Maximum voluntary contraction is determined by using cuffed sphygmomanometer in place of hand grip dynamometer.

The patient lying in supine position blood pressure is recorded. A cuffed sphygmomanometer is inflated and the patient is asked to squeeze the cuff to that of mercury column of sphygmomanometer fixed at the level of 30 % of maximum voluntary contraction for 5 minutes. Blood pressure is recorded on the opposite arm at

the end of 5 minutes.

The response to hand grip test is measured as difference between the diastolic blood pressure at rest and the diastolic blood pressure before the release of grip.

MATERIAL AND METHODS

Sixty patients with mean age of 57.7% who had non insulin dependent diabetes mellitus, varying from one year to fifteen years duration with normal 12 lead electrocardiograph were selected for study.

Clinical signs of cardiac failure electrocardiograph abnormalities of ischemia arrythmias were excluded from study. Those patients who had hypertension congestive cardiac failure ischemic heart disease chronic obstructive pulmonary disease and disease which are known to cause autoimmune dysfunction rheumatoid arthritis leprosy, Gullian-barre syndrome etc were excluded from the study.

The diabetic control of the patient was achieved with diet, oral antidiabetic agents.

The control group consisted of 10 nondiabetic individuals 6 males and 4 females with mean age of 50.1 % who fulfilled all the criteria and in addition had no family history of diabetes mellitus and no symptoms of autonomic dysfunction.

A detailed history physical examination and routine investigations were observed and recorded from all patients as set forth in the pro forma.

The following tests of autonomic function were carried out

Parasympathetic system

1) Heart rate variation to deep breathing
2) Postural variation of heart rate
3) Valsalva test

Sympathetic system

4) Postural variation of blood pressure

5) Hand grip test

DISCUSSION

A study of involvement of autonomic nervous system in 60 patients of non insulin dependant diabetes mellitus (with age less than fifty 19 patients, 29 patients with age group 50 to 60, and 12 patients with age more than 60) and 10 nondiabetic individuals control reveals the following.

In 55% of the patients at least one symptoms of autonomic dysfunction was observed.

POSTURAL GIDDINESS

The commonest symptom observed was Postural giddiness (33%) 20/60.

Correlating with age, 10.5% (2/19) 0f patients with age less than 50 had postural giddiness.

In age group 50 to 60 postural giddiness was found in 31% (9/29)

In patients with age more than 60, postural giddiness was found in 75% (9/12).

Correlating with duration of disease

Patients with duration of diabetes less than five years 12.5% (3/24) had postural giddiness.

Patients with duration of diabetes in-between five to ten years 34.5% (10/29) had postural giddiness.

Patients with duration of diabetes more than ten years 100% (7/7) had postural giddiness.

Sweating abnormality

The second commonest symptom observed was sweating abnormality (30%) 18/60.

Correlating with age, with age less than 50 no patients had sweating abnormality.

In age group 50 to 60 sweating abnormality was found in 37.9% (11/29)

In patients with age more than 60, sweating abnormality was found in 58.3% (7/12).

Correlating with duration of disease

Patients with duration of diabetes less than five years 4% (1/24) had sweating abnormality.

Patients with duration of diabetes in-between five to ten years 44.8% (13/29) had sweating abnormality.

Patients with duration of diabetes more than ten years 57.1% (4/7) had sweating abnormality.

Nocturnal diarrhea and constipation

Nocturnal diarrhea and constipation was observed in 25% (15/60).

Correlating with age, 5% (1/19) 0f patients with age less than 50 had nocturnal diarrhea and constipation.

In age group 50 to 60 nocturnal diarrhea and constipation was found in 27.6% (8/29)

In patients with age more than 60, nocturnal diarrhea and constipation was found in 50% (6/12).

Correlating with duration of disease

Patients with duration of diabetes less than five years no patient had nocturnal diarrhea and constipation.

Patients with duration of diabetes in-between five to ten years 34.5% (10/29) had nocturnal diarrhea and constipation.

Patients with duration of diabetes more than ten years 71.4% (5/7) had nocturnal diarrhea and constipation.

Postprandial fullness of stomach after 2 hours

Postprandial fullness of stomach after 2 hours was observed in 23.3% (14/60).

Correlating with age, 5% (1/19) 0f patients with age less than 50 had postprandial fullness of stomach after 2 hours.

In age group 50 to 60 postprandial fullness of stomach after 2 hours was found in 24.1% (7/29)

In patients with age more than 60, postprandial fullness of stomach after 2 hours was found in 50% (6/12).

Correlating with duration of disease

Patients with duration of diabetes less than five years 4% (1/24) had postprandial fullness of stomach after 2 hours.

Patients with duration of diabetes in-between five to ten years 31% (9/29) had

postprandial fullness of stomach after 2 hours.

Patients with duration of diabetes more than ten years 57.1% (4/7) had postprandial fullness of stomach after 2 hours.

Impotence

Impotence was reported in 13.3% (8/60).

Correlating with age, with age less than 50 no patient reported Impotence.

In age group 50 to 60 Impotence was reported in 13.8% (4/29)

In patients with age more than 60, Impotence was reported in 33.3% (4/12).

Correlating with duration of disease

Patients with duration of diabetes less than five years no patient reported impotence.

Patients with duration of diabetes in-between five to ten years 13.7% (4/29) had reported impotence

Patients with duration of diabetes more than ten years 57.14% (4/7) had reported impotence.

Peripheral neuropathy and Pupilary changes

Peripheral neuropathy was observed in 40% (24/60) of patients.

In 46.6% (28/60) patients Pupilary changes was observed.

In patients with peripheral neuropathy 95.8% (23/24) had Pupilary changes.

Resting tachycardia

Resting tachycardia was observed in 56.7% (34/60).

Postural hypotension

Postural hypotension was observed in 36.7% (22/60).

The results of various tests of autonomic function are as follows. While interpreting the results all borderline cases were considered as normal.

Heart rate variation to deep breathing

Heart Rate (RR Interval) Variation during Deep Breathing

Normal > 15 Border line 10 – 15 Abnormal < 10

Mean of the Control Group 15.23

Mean of the Study Group 12.95

Mean of the Abnormal Group 6.94

S.No	< 10	10 - 15	> 15
1	8.3	11.1	17.3
2	5.5	12.7	29.7
3	6.2	10.7	18.9
4	5.5	11.9	16.9
5	7.4	11.0	20.0
6	8.8	12.1	15.6
7	7.1	13.0	31.2
8	6.2	10.6	17.9
9	7.9	12.5	34.3
10	3.4	10.3	15.9
11	8.3	12.9	16.6
12	5.8	10.7	38.6
13	7.1	12.0	18.8
14	5.8	11.2	28.2
15	6.4	12.7	32.1
16	8.8	14.6	18.2
17	7.4	13.0	
18	6.2	11.9	
19	9.1	12.5	
20	6.7	12.9	
21	8.9		
22	7.7		
23	4.0		
24	8.1		
	166.6	240.3	370.2
	6.94	12.02	23.14
	24/60	20/60	16/60
	40 %	33.33 %	26.66 %

The mean rise of heart rate during inspiration in the study group was 12.95 as against 15.23 in control group.

Rise of heart rate less than ten was observed in 40% of study group with mean of 6.94.

Further 26.7% (16/60) had rise of heart rate in border line range 0f 10 to 15.

II. Postural variation of heart rate

Postural Variation of Heart Rate (30/15)

Normal > 1.03 Border line 1.0 – 1.03 Abnormal < 1.0

Mean of the Control Group 1.06

Mean of the Study Group 1.02

Mean of the Abnormal Group 0.901

S.No	< 1.00	1.00 - 1.03	> 1.03
1	0.960	1.023	1.360
2	0.820	1.030	1.200
3	0.930	1.000	1.680
4	0.890	1.027	1.150
5	0.870	1.025	1.070
6	0.920	1.030	1.200
7	0.960	1.024	1.300
8	0.940	1.029	1.350
9	0.920	1.026	1.380
10	0.880	1.023	1.060
11	0.830	1.027	1.280
12	0.930	1.025	1.330
13	0.890	1.029	1.100
14	0.970	1.000	1.480
15	0.950	1.024	1.220
16	0.947	1.030	1.160
17	0.830	1.026	1.230
18	0.800	1.023	1.110
19	0.830		1.600
20	0.950		1.080
21			1.460
22			1.260
	18.017	18.421	28.060

	0.901	1.023	1.275

The mean value of 30/50 ratio was 1.02 in the study group is compared to 1.06 in control group.

In study group 33.3% (20/60) had 30/15 ratio less than one with mean 0.901.

Further 30% (18/60) of patient in study group had 30/15 ratio in borderline range of 1.00 to 1.03.

III. Valsalva test

Valsalva Ratio

Normal > 1.2 Border line 1.11 – 1.2 Abnormal < 1.11

Mean of the Control Group 1.25

Mean of the Study Group 1.189

Mean of the Abnormal Group 0.997

S.No	< 1.11	1.11 - 1.20	> 1.20
1	1.080	1.130	1.310
2	1.040	1.190	1.310
3	1.100	1.120	1.480
4	1.000	1.150	1.260
5	0.890	1.130	1.260
6	0.920	1.140	1.380
7	1.074	1.160	1.310
8	0.950	1.185	1.320
9	1.100	1.192	1.310
10	0.960	1.115	1.460
11	0.930	1.125	1.280
12	1.070	1.160	1.430
13	0.890	1.130	1.230
14	1.027	1.140	1.350
15	0.940	1.111	1.430
16	1.030	1.192	1.240
17	1.000		1.330
18	0.950		1.480
19			1.380
20			1.310
21			1.480
22			1.310
23			1.350
24			1.460
25			1.330
26			1.230
	17.951	18.370	35.020

	0.997	1.148	1.347

The mean value of Valsalva ratio was 1.189 in the study group is compared to 1.256 in control group.

In study group 30% (18/60) with mean 0.997 had Valsalva ratio less than 1.11.

Further 26.7% (16/60) of patient in study group had Valsalva ratio in borderline range of 1.22 to 1.2.

IV. Postural variation of blood pressure

Postural hypotension

Fall in systolic blood pressure

Normal <= 10 mm/Hg

Border line 11-29 mm/Hg

Abnormal >= 30 mm/Hg

Mean of the Control Group -9.8 mm/Hg

Mean of the Study Group -20.86 mm/Hg

Mean of the Abnormal Group -34 mm/Hg

S.No	**>= 30**	**11 - 29**	**<= 10**
1	-30	-24	-10
2	-36	-18	-8
3	-38	-12	-6
4	-36	-20	-8
5	-34	20	-6
6	-38	-18	-10
7	-40	-16	-10
8	-32	-12	-6

9	-32	-20	-10
10	-30	-14	-8
11	-38	-16	-10
12	-34	-12	-6
13	-30	-18	
14	-36	-20	
15	-38	-14	
16	-36	-18	
17	-34	-24	
18	-32	-16	
19	-34	-18	
20	-30	-12	
21	-36	-16	
22	-32	-14	
23		-20	
24		-18	
25		-12	
26		-16	
	-756	-398	-98
	-34	-15	-8

In the study the mean fall of blood pressure on standing was -20.86 millimeter of mercury as compared to 9.8 millimeter of mercury in control group.

Among the patients 36.7% (22/60) had fall in blood pressure of more than 30 millimeter of mercury.

Further 26.7% (26/60) of patient in study group had borderline fall between 11 and 29 millimeter of mercury.

V. Hand grip test

Blood pressure response to sustained hand grip

Normal<= 10 Border line 11-16 Abnormal >= 16

Mean of the Control Group 16.4

Mean of the Study Group 11.7

Mean of the Abnormal Group 8.14

S.No	<= 10	11 - 16	>= 16
1	6	14	16
2	10	12	18
3	8	14	16
4	6	12	16
5	10	12	18
6	10	14	16
7	6	14	16
8	6	14	18
9	8	12	18
10	10	14	16
11	8	12	16
12	8	12	16
13	10	14	18
14	6	14	16

15	10	12	
16	10	12	
17	8	14	
18	6	12	
19	10		
20	6		
21	6		
22	10		
23	8		
24	10		
25	6		
26	8		
27	8		
28	10		
	228	234	234
	8.143	13	16.714

The mean rise in diastolic blood pressure in study group was 8.14 as compared to 16.4 in control group.

Among the patients 46.7% (28/60) had rise of blood pressure less than 10 millimeter of mercury.

Further 23.3% (14/60) had borderline rise of blood pressure between 10 and 16 millimeter of mercury.

Control group:

Control Group					
S.No	Hand Grip Test	BP Variation of HR	Postural Variation of HR	Valsalva Ratio	Postural Variation Of BP
1	16	13.80	1.14	1.38	-6.0
2	18	10.50	1.06	1.20	-4.0
3	16	17.20	1.10	1.12	-12.0
4	18	17.40	1.00	1.43	-16.0
5	14	23.80	1.04	1.20	-8.0
6	16	11.20	1.10	1.14	-12.0
7	16	18.20	1.05	1.25	-12.0
8	18	17.40	1.00	1.18	-16.0
9	14	10.50	1.04	1.53	-4.0
10	18	12.30	1.10	1.13	-8.0
	164	152.30	10.63	12.56	-98.0
	16.4	15.23	1.06	1.256	-9.8

CONCLUSION

The exact prevalence of autonomic neuropathy in diabetes is precisely not known, however tests of autonomic function have shown impairment in roughly 40 to 50% of diabetic patients.

Subclinical autonomic nerve damage occurs more widely in diabetes and may go unnoticed. It is assuming greater importance because of the implications for morbidity and mortality.

Symptomatic autonomic neuropathy carries worse prognosis than any other complication of diabetes.

Prevention of autonomic damage with newer drugs, particularly in its earlier stage will reduce the mortality and morbidity significantly.

Newer drugs have to be tried for comforting many diabetics with clinical autonomic neuropathy afflicted with this condition in that atleast the quality of life of with diabetic neuropathy will improve.

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PROFORMA

STUDY OF CLINICAL PRESENTATION OF AUTONOMIC NEUROPATHY IN PATIENTS WITH DIABETES MELLITUS

Name :

Age : Sex : IP / OP. No. :

Clinical Data: Diabetes mellitus

Duration of diabetes

History

- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Fatigue
- Skin infection
- Periarthritis shoulder
- Balanitis/ pruritis vulva

Clinical data: Autonomic neuropathy

- Persistent fullness of stomach 2 hours after meals
- Nocturnal diarrhea
- Constipation

- Bladder distension
- Post void residual urine
- Erectile dysfunction
- Light headedness on standing
- Syncope on standing
- Postprandial hyperhydrosis of upper extremitie and anhydrosis of lower extremities

Clinical data: Peripheral Neuropathy

- Numbness
- Paresthesias
- Hyperesthesia

Past history

- Hypertension
- Ischemic heart disease
- STD
- Prostate enlargement
- Urethral stricture

Treatment history

- Oral hypoglycemic agents
- Insulin

Family history

General examination

- Pallor
- Icterus
- Cyanosis
- Clubbing
- Lymphadenopathy
- Edema

Vital data

- Pulse
  - Lying
  - Standing
- Blood pressure
  - Lying
  - Standing
- Respiratory rate
- Temperature

Cardiovascular system

- Jugular venous pressure
- Heart sounds

- Murmur

Respiratory system

- Breath sounds
- Added sounds

Abdomen

- Bowel sounds
- Free fluid
- Liver/spleen

Nervous system

- Peripheral neuropathy
- Any focal neurological deficit

Pupil

- Size
- Shape

Light reflex

- Accommodation

Tests for Autonomic neuropathy

A. Heart rate variation to deep breathing

B. Postural variation of heart rate

(RR interval of 30^{th}beat/15^{th}beat)

C. Valsalva test

(Longest RR interval after maneuver/shortest RR interval during maneuver)

D. Postural variation of blood pressure

Supine BP (3 min rest) to BP immediately in erect posture

E. Hand grip test (diastolic blood pressure variation > 16mm)

(30 % of maximum voluntary contraction for 5 min)